REMARKS

Prior to the present amendment, Claims1-10, 13-18, 21-29, 32-36, 44, 45, 48-68 and 75-78 were pending. In this amendment Claims 1, 14, 18, 28, 44, 60, 61, and 62 are amended. Claims 53-59 are cancelled. Claims 1-10, 13-18, 21-29, 32-36, 44-45, 48-52 and 60-78 remain in prosecution.

This is a complex case and Applicants greatly appreciate the very significant efforts the Examiner has made to understand the technology and give the application a fair examination.

These comments are partially based on the Interview of 1 July 2004 as supported by the newly submitted declaration of Dr. Ljubimova.

Rejections under 35 U.S.C. 112, first paragraph—Written Description.

In the Office Action the Examiner repeated the rejection of Claims 1-10, 13-18, 21-29, 32-36, 44-45, 48-68 and 75-78 under 35 U.S.C. 112, first paragraph as containing subject matter not described in the specification in such a way as to enable on skilled in the art to make and/or use the invention. It appears that the primary problem here is the extreme breadth that the Examiner sees in claims drawn to "*laminin α4*-specific mRNA." The present invention is based on the discovery that malignancies overexpress *laminin α4*-specific mRNA and that this overexpression directly leads to more aggressive and spreading tumor. Thus, the Applicants are convinced that while mRNA expression is of diagnostic significance, this significance depends on the actual participation of the laminin α4-subunit in mature laminin proteins. It is believed that all the possible variations in mRNA are not operational in the system but

must encode a functional laminin α4-subunit to be operational. That is, the claims talk about detecting an mRNA and while a given mRNA might be detected using probes of various sequences, etc., that detection is of little significance unless the detected mRNA encodes a function laminin α4-subunit because unless there is a functional subunit, the malignancy will not be enhanced. Applicants believe that this situation is readily distinguished from *The Regents of the University of California v. Eli Lilly* because in that case the applicants were trying to claim a composition of matter based on generic function. In the current case we have a method and a step in the method is to detect a certain class of mRNA. No composition is being claimed, and it is relatively straightforward for one of skill in the art to determine whether the mRNA in question is capable of encoding a functional laminin α4-subunit through methods taught in the specification such as immunohistochemical methods, etc. While it is appreciated that Genebank Numbers may change with time, a laminin α4- subunit has a very clear definition and one of skill in the art could readily obtain sequence information for it.

In the Interview the Examiner indicated that if it were made clear that a "functional" laminin α4- subunit was essentially equivalent to the known laminin sequence as mentioned in Example 2 of the application (GeneBank sequence Z99289), the enablement rejection would be withdrawn. Applicant has checked the database to make certain that the currently available sequence is the same as the one referred to in the original application. Appended hereto is the report page from GeneBank indicating that the currently available sequence was entered into the database in 1998 and has not changed. The specification has been amended to insert SEQ ID NO:1 as being identical to Z99289. Further, the other SEQ ID NOs have been corrected

to reflect this addition. SEQ ID NO:1 (Z99289) has been electronically submitted to the PTO as a computer readable revised sequence listing.

Finally, the claims have been amended to refer to SEQ ID NO:1. With these changes, Applicants believe that the Written Description is now satisfied for the amended claims. Considering that the Examiner has already agreed that the method is enabled for gliomas, Claim 18, at the very least, should be allowable.

Rejections under 35 U.S.C. 112, first paragraph—Written Description.

In the Office Action the Examiner repeated the rejection of Claims 1-10, 13-18, 21-29, 32-36, 44-45, 48-68 and 75-78 under 35 U.S.C. 112, first paragraph because the Examiner considered the claims enabled for gliomas but not for other malignant tumors. In discussing Applicants previous remarks and Declaration (page 11 of the Office Action), the Examiner observes: "Thus, the evidence provided in the declaration may support that metastasized tumors from the brain also show an increased level of alpha4, however, they do not illustrate that alpha4 is overexpressed in breast cancer." This statement seems to based on the misapprehension of the Examiner concerning the data presented in the Declaration. The Declaration presents data on two types of breast cancer: namely from primary breast cancer tumors (i.e., those within the breast) and from secondary breast cancer tumors that have metastasized outside of the breast (in this case into the brain). Both the primary and metastasized tumors clearly show an elevation in laminin $\alpha 4$.

There is no possibility of mistaking breast cancer for brain cancer because all of these samples are analyzed histologically and the tissue differences between breast cancer and brain cancer are unmistakable. Further,

while breast cancer may metastasis to many other organs, primary brain cancer is not capable of metastasizing outside of the brain. A Supplemental Declaration has been submitted showing additional normal breast data and explaining some apparent discrepancies remarked upon by the Examiner. In brief, breast biopsies are more complex tissue wise than brain samples. In particular, normal ductal tissues show laminin $\alpha 4$ expression, but this is almost entirely in the form of Laminin 9. The correlation of Laminin 8 with invasive malignancies is clear for breast tissue. Since these two types of cancer are remarkably dissimilar in structure as well as cellular origin, it is reasonable to expect that diverse malignancies to show similar results. Preliminary data suggest this for prostate cancer but as covered during the Interview, only relatively non-invasive prostate cancers have been analyzed to date. While Applicants believe that the written description is enabled not only for gliomas and breast cancer but for other malignancies as well, it is possible to interpret the data as supporting "invasiveness" detection only. Therefore, claim 60 has been amended to claim this feature.

Other Matters

In an effort to simplify this prosecution and move the case forward Applicant has amended the claims directed towards a grading system. While Applicants continue to believe that the application contains adequate data to allow one of skill in the art to implement a grading system, Applicants also recognize validity in some of the Examiner's points. Therefore, the claims directed towards a grading system have been cancelled. The main trust of the instant application is to detect malignancies and to predict the reoccurrence of invasive gliomas that have been resected. Applicants believe that the data supporting these claims are clear and intend to focus the prosecution on those claims.

Further, the Examiner is correct that Claims 44 and 53 are substantially identical. Claim 53 and its dependent claims have also been cancelled.

In view of the foregoing, it is respectfully submitted that the application is in condition for allowance. Reexamination and reconsideration of the application, as amended, are requested. If for any reason the Examiner still finds the application other than in condition for allowance, the Examiner is requested to call the undersigned attorney at the Los Angeles telephone number (310) 500-3548 to discuss the steps necessary for placing the application in condition for allowance.

You are hereby authorized to charge any fees due and refund any surplus fees to our Deposit Account No 50-2899.

Respectfully submitted,

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Date: 28 July 2004

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Attachment: Second Declaration of Julia Lubimova
NCBI information page on Accession Z99289